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(54) Title: STEREOSELECTIVE SYNTHESIS OF 2-HYDROXY-4-PHENYLBUTYRIC ACID ESTERS

*

$$Ph\text{---}CH_2\text{---}CH_2\text{---}CH(OR^2)\text{---}COOR^1 \qquad (I)$$

*

$$Ph\text{---}CH_2\text{---}CH_2\text{---}CH(OH)\text{---}CN \qquad (II)$$

(57) Abstract: A process is described for the stereospecific preparation of an ester of formula (I): wherein *signifies the (R) stereoisomer; R^1 is selected from C_{1-6} alkyl, preferably ethyl; and R^2 is hydrogen, a protecting group or a leaving group which process comprises reaction of a nitrile of formula (II): wherein *signifies the (R) stereoisomer; and Ph is the phenyl group C_6H_5 with a solution of an inorganic acid in an alcohol and optional conversion of the compound of formula (I) wherein R^2 is H so prepared to any other desired compound of formula (I) by standard methods in the art. The compounds of formula (I) are chiral esters, useful as intermediates in the synthesis of the family of acetylcholine esterase (ACE) inhibitors known as 'prils', such as lisinopril, cilazapril, enalapril, benazepril, ramipril, delapril, enalaprilat, imidapril, spirapril, trandolapril and others.

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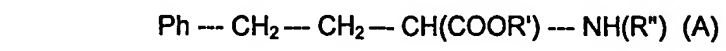
STEREOSELECTIVE SYNTHESIS OF 2-HYDROXY-4-PHENYLBUTYRIC ACID ESTERS

The present invention relates to a process for the synthesis of chiral compounds, and in particular chiral esters, for use as intermediates in the synthesis of the family of acetylcholine esterase (ACE) inhibitors known as 'prils'.

The 'prils' have the general formula (A):



$$Ph\text{---}CH_2\text{---}CH_2\text{---}CH(COOR')\text{---}NH(R'') \quad (A)$$

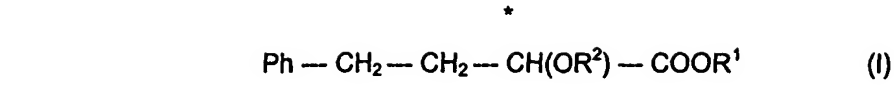
wherein R' is hydrogen or C_1-C_2 alkyl and R" is selected from a large number of possible moieties. Examples of 'prils' include lisinopril, cilazapril, enalapril, benazepril, ramipril, delapril, enalaprilat, imidapril, spirapril, trandolapril and others.

These 'pril' compounds are chiral compounds, only one of their diastereomers being pharmacologically active. It is therefore necessary to isolate and purify the active diastereomer, rather using a racemic mixture, for pharmaceutical/medical applications.

Typically, separation of diastereomers is carried out by preferential crystallisation, for example as described in US patent specification no. 5,616,727. However, the yields of such crystallisations are often low and, indeed, the yield from the process used in US patent specification no. 5,616,727 was only 68%.

Alternatively, a stereochemical synthesis may be used, wherein various intermediates used in the preparation of the 'prils' are, in turn, prepared in chiral form, which results in a predominance of the desired diastereomer in the final 'pril' product. However, such chiral syntheses are complex and the yields are also unsatisfactory.

The present invention relates to an improved, stereospecific process for the synthesis of an intermediate for making 'pril' compounds. This intermediate can be converted to the required 'pril' isomer, or any other desired end-product, without loss of stereospecificity. The intermediate of interest is an ester of formula (I):



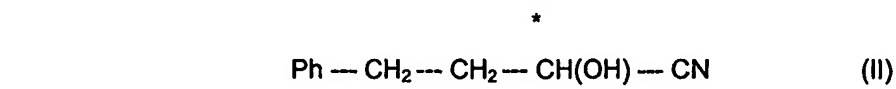
$$Ph - CH_2 - CH_2 - CH(OR^2) - COOR^1 \qquad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group.

Suitable leaving groups R^2 include p-toluene sulphonyl (tosyl), methane sulphonyl chloride (mesyl), trifluoromethane sulphonyl (triflic), and p-nitrobenzene sulphonyl.

Suitable protecting groups R^2 include *tert*-butyl dimethyl siliyl (TBDMS), TMS, BOC and the like.

One method of stereospecific synthesis involves the conversion of the compound (R)-2-hydroxy-4-phenylbutyronitrile having the formula (II):



$$Ph - CH_2 - CH_2 - CH(OH) - CN \qquad (II)$$

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group C_6H_5
to the corresponding ester of formula (I).

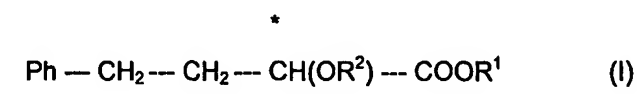
In Tet. Lets. 30 (15) 1917-20 (1989) is disclosed the above process to produce a compound of formula (I) wherein R^2 is H and R^1 is ethyl. However, the method described involves a three-stage process, resulting in a yield of only 78%, based on the nitrile of formula (II). The three process steps are: (i) treating the nitrile (II) with dihydopyran in pyridinium p-toluene sulphonate to prepare the THP derivative; (ii) hydrolysing the nitrile group with sodium hydroxide; and, finally, treating the resulting acid with anhydrous ethanol and a catalytic amount of concentrated sulphuric acid.

We have therefore looked at the possibility of using alternative methods of synthesising this ester, but none of these appeared to provide the desired combination of high *ee* (*eg* 97-98%); economic reaction time; acceptable yields (*eg* > 80%); and overall ease of handling and commercial viability of the process.

Instead, we have surprisingly found that, by careful selection of novel reaction conditions and reagents, we can obtain the desired *ee* in high yields and under commercially-acceptable conditions, involving a so-called 'one-pot' reaction, in which the reaction appears to go in one step, without the addition of further reagents or reactants, but with the formation of an unstable intermediate that need not be isolated but converts *in situ* to the desired compound of formula (I).

The novel one-pot reaction according to this invention involves reacting the nitrile of formula (II) with an alcoholic solution of an inorganic acid, such as sulphuric acid or hydrochloric acid, to give the ester of formula (I) *via* an *in situ* conversion.

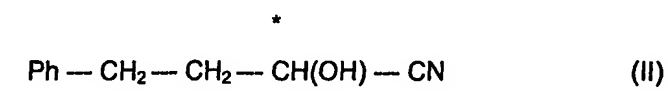
There is therefore provided a process for the stereospecific preparation of an ester of formula (I):



(I)

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of a nitrile of formula (II):



(II)

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group C_6H_5
with a solution of an inorganic acid in an alcohol
and optional conversion of the compound of formula (I) wherein R^2 is H so prepared to any other desired compound of formula (I) by standard methods known to those skilled in the art.

Accordingly, the present invention further provides a process for preparing a compound of formula (I), which process comprises reaction of an intermediate imine of formula (III):

$$[Ph — CH_2 — CH_2 — CH(OR^2) — CH{=}NH.HX] \qquad (III)$$

in which R^2 is as defined in formula (I); and X is the anion of an inorganic acid, such as sulphate or halide, preferably halide, more preferably chloride, with an alcohol of formula R^1OH, in which R^1 is as defined in formula (I).

It is preferred that R^1 is C_1-C_4 alkyl, for example methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl or *tert*-butyl. Accordingly, ethanol is the preferred alcohol. Conveniently, the alcoholic solution of the acid is prepared by bubbling dry, gaseous acid into absolute alcohol. Preferable, the solution comprises at least 4-5% w/v of acid (gas), more preferably > 7%w/v, such as in the range of from 7-15% w/v, based on grams of acid per 100ml of alcohol.

It is preferred that the alcohol/acid solution be as anhydrous as possible, in order to ensure that the ester is formed in preference to the corresponding acid. The reaction may be carried out at a temperature in the range of from 0 to 80 °C, such as at reflux temperature of the reaction mixture, at atmospheric pressure. For example, using the ethanol/HCl, the reaction may be carried out at 70-85 °C over a period in the range of from 12 to 20 hours, such as at 75-80°C over a period of 15 hours, or for 2 hours at 10-15 °C followed by refluxing for 15 hours, all at atmospheric pressure. The skilled chemist will be able to adjust the temperature/pressure/reaction period factors appropriately.

The ratio of nitrile of formula (II): acid/alcohol solution is in the range of from 1:6 to 1:10, preferably about 1:8, by volume.

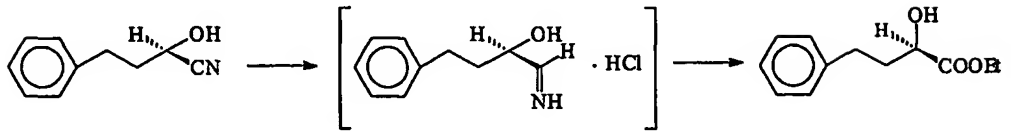
The yield of this reaction is about 80% of theoretical with an enantiomeric excess (*ee*), based on optical rotation, of the (R) isomer of about 97%.

The present invention therefore further provides an ester of formula (I), in particular, an ester of formula (I) comprising at least 97% of the (R) isomer, whenever prepared by a process according to this invention; and such a compound (I) for use in, or whenever used in, the preparation of a stereospecific 'pril' of formula (A).

Furthermore, there is provided a method for the preparation of a stereospecific 'pril' of formula (A), which method comprises preparation of an ester of formula (I) by a process according to this invention; and a stereospecific 'pril' of formula (A), whenever prepared by such a process.

The invention will now be described in more detail with reference to the following non-limiting examples.

Example: Preparation of (R)-2-Hydroxy-4-phenyl butyric acid



(R)-isomer (R)-isomer

(II) (III) (I)

(a) Preparation of alcoholic HCl (g)

To 1 kg of common salt (NaCl) was added 250 ml of concentrated sulphuric acid, dropwise at room temperature. The hydrogen chloride gas evolved was first passed through a trap containing concentrated sulphuric acid to dry it and then passed with stirring into absolute alcohol (2l) which was kept at 0-5°C. The process was carried out for 4-6 hours until the required strength was obtained.

(b) Preparation of Title Compound

To (R)-2-hydroxy-4-phenyl-butyronitrile ((II), 250g, 1.55 M) was added absolute alcohol (2l) which contained at least 7% w/v of dry hydrogen chloride gas at 10-15°C. The mixture was stirred for 2 hours at the same temperature. This was carried out to allow confirmation of the conversion of the nitrile to the corresponding imine hydrochloride. After this, the reaction mass was refluxed at 75-80°C. The reaction was monitored using TLC and after 15 hours was found to be complete.

The alcohol was removed from the reaction mass *in vacuo* at 55-60°C. The resulting residue was taken in water (1l) and extracted with dichloromethane (500 ml x 2). The collective organic phases were dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield a reddish, thick liquid. This was vacuum-distilled to obtain the desired product in 78-80% yield (of theoretical), as a colourless liquid.

The whole process can be summarized as follows :

Substrate	Substrate in Ethanolic HCl	HCl concentration	Temp	Time	Yield	Purity by HPLC
(R)-2-Hydroxy-4-phenylbutyronitrile	1 : 8 by volume	7-15% w/v	75-80°C	15 hrs	78-80% of theoretical	98%

Analytical data :

$^{20}[\alpha]_D$: -10 at 100% concentration (solvent free).

Reported $^{20}[\alpha]_D$: -10 ± 1 at 100% concentration (solvent free).

Boiling point: 125-127°C at 1mm Hg to 2 mm Hg vacuum; 120°C at 1.5 mm

NMR (Varian^{RTM} 60 MHz): (CCl_4, TMS) 7.3 (S, 5 H), 3.8-4.3 (m, 3 H), 2.5 – 2.8 (t, 3 H), 1.4-2 (m, 2 H), 1-1.3 (t, 3 H)

Density: 1.0751

Refractive index: 1.502

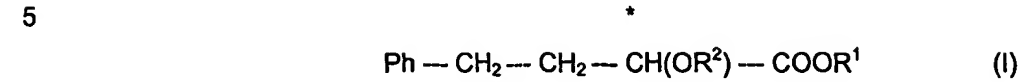
HPLC 1: Column C_{18} (250 mm X 4.6 mm X 5 μ); mobile phase: methanol : H_2O (80 : 20); wavelength: 210 nm; flow rate: 1 ml/min; retention time: 4.17 minutes

HPLC 2: Column C_{10} Si 60 (5 μm) (250 mm X 4.0 mm X 5 μ); mobile phase: hexane : ethyl acetate (90 : 10); wavelength: 254 nm; flow rate: 1.0 ml/min; retention time: 21.60 minutes

IR: OH 3400 cm^{-1} – 3500 cm^{-1}; C=O 1750 cm^{-1}

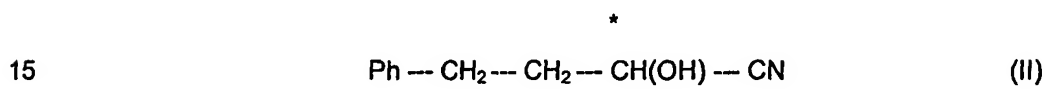
CLAIMS

1. A process for the stereospecific preparation of an ester of formula (I):



wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of a nitrile of formula (II):



wherein * signifies the (R) stereoisomer; and Ph is the phenyl group C_6H_5
with a solution of an inorganic acid in an alcohol
and optional conversion of the compound of formula (I) wherein R^2 is H so prepared to any other desired compound of formula (I).

2. A process according to claim 1, wherein the acid is hydrogen chloride (gas).

3. A process according to claim 1 or claim 2, wherein the alcohol is ethanol.

4. A process according to any preceding claim, wherein the reaction is carried out substantially in the absence of water.

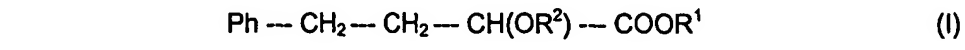
5. A process according to any preceding claim, wherein the acid/alcohol solution comprises >7% w/v of the acid (gas), based on the volume of the solution.

6. A process according to any preceding claim, wherein the reaction is carried out at the reflux temperature of the alcohol.

7. A process according to any preceding claim, wherein the reaction is carried out at 70-85 °C and goes to completion in the range of from 12 to 20 hours.

8. A process according to any preceding claim, wherein the ratio of nitrile of formula (II): acid/alcohol solution is in the range of from 1:6 to 1:10, preferably about 1:8, by volume.

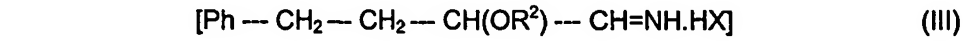
9. A process for the stereospecific preparation of an ester of formula (I):



$$Ph --- CH_2 --- CH_2 --- CH(OR^2) --- COOR^1 \quad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of an intermediate imine of formula (III):



$$[Ph --- CH_2 --- CH_2 --- CH(OR^2) --- CH{=}NH.HX] \quad (III)$$

in which R^2 is as defined in formula (I); and X is the anion of an inorganic acid, such as halide, preferably chloride, with an alcohol of formula R^1OH, in which R^1 is as defined in formula (I)

10. A process according to claim 9, wherein R^1 is ethyl.

11. A process according to claim 9 or claim 10, wherein the reaction is carried out substantially in the absence of water.

12. An ester of formula (I), comprising at least 97% of the (R) isomer, whenever prepared by a process according to any preceding claim.

13. An ester according to claim 12 for use in, or whenever used in, the preparation of a stereospecific 'pril' of formula (A).

14. A method for the preparation of a stereospecific 'pril' of formula (A), which method includes the preparation of an ester of formula (I) by a process according to any of claims 1 to 11.

15. A stereospecific 'pril' of formula (A), whenever prepared by a process according to claim 14.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/IB 02/01689

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C67/22 C07C69/732 C07C69/734 C07C229/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG Y-F ET AL: "LIPASE-CATALYZED IRREVERSIBLE TRANSESTERIFICATION USING ENOL ESTERS RESOLUTION OF CYANOHYDRINS AND SYNTHESES OF ETHYL-R-2-HYDROXY-4-PHENY LBUTYRATE AND S PROPRANOLOL" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 30, no. 15, 1989, pages 1917-1920, XP002179194 ISSN: 0040-4039 cited in the application	12,13
A	page 1919; figure 2	1,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2002	11/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kardinal, S

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PCT/IB 02/01689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	URBACH, H ET AL.: "A favourable diastereoselective synthesis of N-(1-S-ethoxycarbonyl-3-phenylpropyl)-S-alanine" TETRAHEDRON LETTERS., vol. 25, no. 11, 1984, pages 1143-1146, XP002211190 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039	12,13
A	page 1143 page 1145; figure II	14
X	WO 00 17228 A (REIDER PAUL J ;SUN YONGKUI (US); HUFFMAN MARK A (US); LEBLOND CARL) 30 March 2000 (2000-03-30) example 1	15
A	HIROMICHI OHTA ET AL.: "Preparation of optically active alpha-hydroxy acid derivatives by microbial hydrolysis of cyanohydrins" AGRICULTURAL AND BIOLOGICAL CHEMISTRY., vol. 55, no. 7, 1991, pages 1877-1881, XP002211188 JAPAN SOC. FOR BIOSCIENCE, BIOTECHNOLOGY AND AGROCHEM. TOKYO., JP ISSN: 0002-1369 page 1878; table II entry 1b, 2b	1,9,14
A	EFFENBERGER, F. ET AL.: "Stereoselective synthesis of 2-amino-4,5-dihydroxyaldehydes" TETRAHEDRON: ASYMMETRY., vol. 11, 2000, pages 1085-1095, XP002211189 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0957-4166 page 1087; figure 2	1
A	GOEHRING W ET AL: "SYNTHESIS OF THE HIV-PROTEINASE INHIBITOR SAQUINAVIR: A CHALLENGE FOR PROCESS RESEARCH" CHIMIA, AARAU, CH, vol. 50, no. 11, 1996, pages 532-537, XP000889687 ISSN: 0009-4293 page 535, paragraph 4.1 scheme 5: 35->36	1

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/01689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HIROYUKI MINAMIKAWA ET AL: "Asymmetric Hydrocyanation of Aldehydes Using Chiral Titanium Reagents" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN., vol. 61, no. 12, December 1988 (1988-12), pages 4379-4383, XP002100390 JAPAN PUBLICATIONS TRADING CO. TOKYO., JP ISSN: 0009-2673 page 4382 hydrolysis of 3c	1
A	US 5 552 317 A (HOUNG JER-YIING ET AL) 3 September 1996 (1996-09-03) the whole document	14,15

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/IB 02/01689

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		EP 1115741 A2	18-07-2001
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